IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of
Osamu JOHDO et al.
Serial No. 09/555,494 Group Art Unit 1634
Filed: June 1, 2000 Examiner: Bradley L. Sisson
For: CRYSTALLINE ANTHRACYCLINE ANTIBIOTIC
AND PROCESS FOR PRODUCING THE SAME

DECLARATION UNDER 37 C.F.R. §1.132

Honorable Commissioner of
Patent and Trademarks
Washington, D.C.

Sir:

I, Osamu JOHDO, one of the applicants in the above-captioned application hereby declare that:

1. I am a Japanese citizen residing at Kameino 3-18-12, Fujisawa, Kanagawa-ken 252-0813, Japan. Since 1988, I have been employed by Mercian Corporation as an engineer, where I have principally engaged in the research in the field of process design and development of bulk pharmaceutical compounds. In December 1993, during my service with the same company, I obtained a doctorate for "Study on new rhodomycin-group of anthracycline antibiotics" from Hiroshima University.

2. I am familiar with the above-captioned application Serial No. 09/555,494. In order to establish the difference in properties between "the currently available bulk form of DM hydrochloride" as mentioned in the specification of the present application, page 1, lines 28 ~ 31, and the reddish-brown crystalline powder of DM hydrochloride of the present invention, the following experiments were carried out under my direction and supervision.

3. For the above-mentioned bulk form of DM hydrochloride, I utilized one which had been obtained by the process as mentioned in "Drug product standard code" Note 1), specifically according to the treatment scheme as mentioned in APPENDIX-A hereto.

Note 1): Said code covers the content of DMF (Drug Master File) which was submitted by the above-mentioned Mercian Corporation, on March 6, 1996, to the F. D. A. (Food and Drug Administration of the United

States Department of Health and Human Services), and was received thereby. To this DMF, an accession number "DMF No. 11879" has been allotted.

4. (1) A powder which had been obtained according to the treatment scheme as mentioned in APPENDIX-A was measured by X-ray powder diffraction method in the same manner as in Example 2 at page 6 of the present specification. Results of this measurement are shown in the measurement chart which is attached hereto as APPENDIX-B. As is seen in this APPENDIX-B, X-ray powder diffraction analysis of powder from the above-mentioned bulk form gives 2θ values as follows:

2θ values: 5.28, 6.62, 7.42, 8.30, 9.06, 9.26, 9.80, 10.44, 11.68 and 12.84

Similar analysis of the powder from the above-mentioned Example 2 of the present invention gives 2θ values as follows:

2θ values: 6.18, 7.88, 9.82, 11.60, 13.30, 15.80, 20.88 and 23.12
(see: the present specification, page 3, lines 17–18, and "b)" in FIG. 1)

As is clearly seen from a comparison between the above-mentioned two sets of 2θ values, and from a comparison between the chart of APPENDIX-B and "b)" in FIG. 1, the powder from the above-mentioned bulk form which had been available before the present invention was made (hereinafter referred to as "the former") is clearly distinguishable from the powder of the present invention (hereinafter referred to as "the latter"). For instance, a peak for "2θ = 11.68 (NR. 9)" which is observed in the chart of the former corresponds to a peak for "2θ = 11.60" in the latter. In the former, however, there is observable almost no peak for "2θ = 9.80 (NR. 7) and 10.44 (NR. 8)", while, in the latter, a very large and remarkable peak is observed for "2θ = 9.82", in which respect the former and the latter are quite different from each other.

(2) The following are results of "test for chemical stability" (in accordance with Example 13 of the present specification) and "test for hygroscopicity (Example 12)" of these two powders:

Stability (% of remaining DM)
Former (after stored at 40°C for one month): 99.1 %
Latter (after stored at 60°C for one month): 100.0 %
(see Table 2 of the present specification)

Hygroscopicity (critical relative humidities)
Former: about 46 %
Latter: about 73 % (see Table 1 of the present specification)

With regard to chemical stability, the latter underwent no decomposition at all after stored at 60°C for one month, and remained 100 %, while the former suffered a slight decomposition (0.9 %) even after stored at a lower temperature (40°C) for one month.

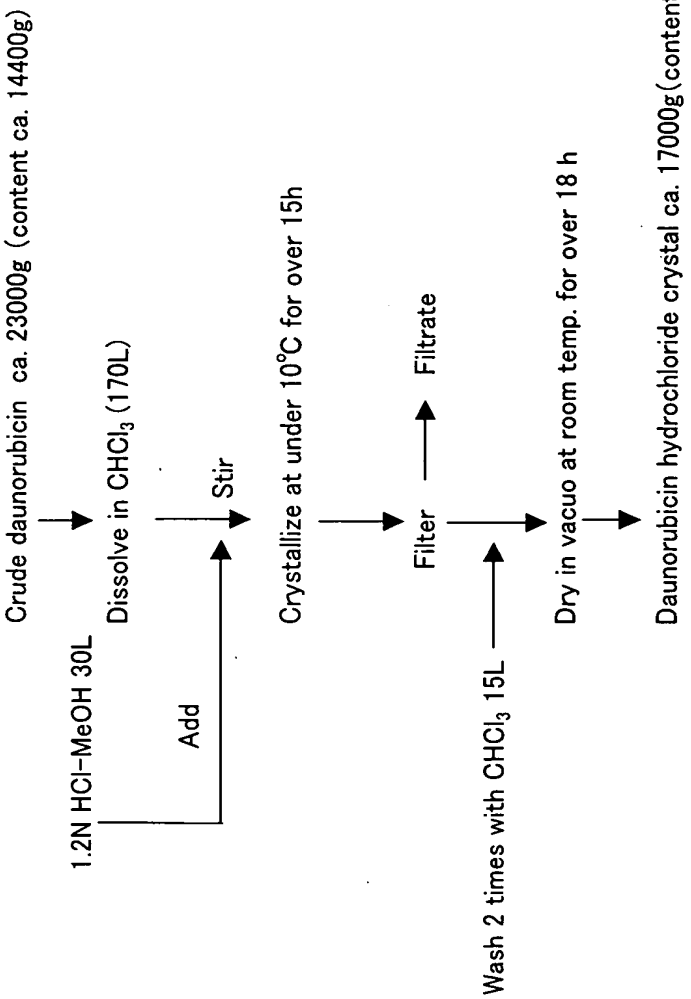
With respect to critical relative humidities, on the other hand, the latter gave a value of 73 % while the former gave a value of about 46 %. It would be evident, therefore, that the crystalline powder of DM hydrochloride of the present invention is different, also in hygroscopicity, from the above-mentioned powder from bulk form.

(3) As stated in the above (1) and (2), the crystalline form of powder of the present invention is quite distinguishable from that of the powder which had been available before the present invention was made.

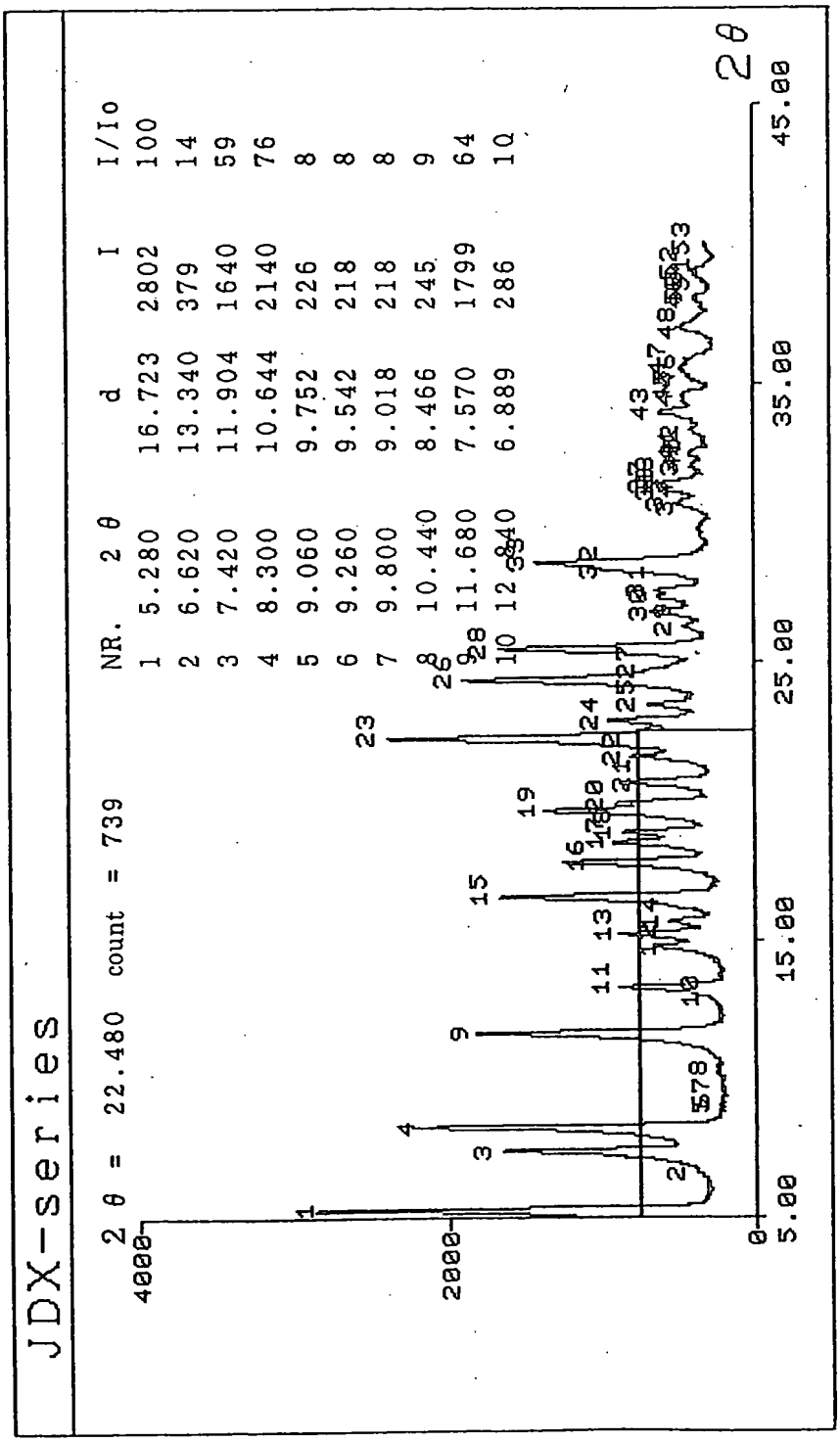
5. The undersigned declarant declares further that all statements made herein of his knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issuing thereon.

Signed this 1st day of December, 2003

APPENDIX-A


Crude daunorubicin ca. 23000g (content ca. 14400g)
1.2N HCl-MeOH 30L
Dissolve in $CHCl_3$ (170L)
Add
Stir
Crystallize at under 10°C for over 15h
Filter
Filtrate
Wash 2 times with $CHCl_3$ 15L
Dry in vacuo at room temp. for over 18 h
Daunorubicin hydrochloride crystal ca. 17000g(content ca. 12200g)

APPENDIX-B


JDX-series
2 θ = 22.480 count = 739
NR. 2 θ d I I/Io
1 5.280 16.723 2802 100
2 6.620 13.340 379 14
3 7.420 11.904 1640 59
4 8.300 10.644 2140 76
5 9.060 9.752 226 8
6 9.260 9.542 218 8
7 9.800 9.018 218 8
8 10.440 8.466 245 9
9 11.680 7.570 1799 64
10 12.340 6.889 286 10
4000
2000
0
5.00
15.00
25.00
35.00
45.00
2θ